DELETION OF INVENTORS

Please correct the inventorship under 37 CFR §1.48(b) by removing the following inventors from the present application:

Dan L. Eaton, Ellen Filvaroff, Mary E. Gerritsen, and Colin K. Watanabe.

REMARKS

The specification has been amended to capitalize trademarks and remove reference to embedded hyperlinks.

Applicants have amended Claims 1-10 to remove reference to the Figures. Claims 1-5 have been amended to add the limitation that the claimed polypeptides are more highly expressed in normal stomach, lung, rectal or skin tissue compared to stomach, lung, rectal or melanoma tumor respectively, or are encoded by a polynucleotide that is more highly expressed in normal stomach, lung, rectal or skin tissue compared to stomach, lung, rectal or melanoma tumor respectively. Applicants maintain that the amendments add no new matter and are fully supported by the specification as originally filed. For example, support for the amendments to Claims 1-5 can be found in Example 18 beginning at paragraph [0529], as well as paragraph [0336] of the specification.

Claims 1-13 are presented for examination. Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed August 3, 2004. For the reasons set forth below, Applicants respectfully traverse.

Correction of Inventorship under 37 CFR §1.48(b)

Applicants request that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

Priority Determination

Applicants acknowledge that the PTO has granted the present application the priority date of **August 24, 2000**. Applicants note that SEQ ID NO: 74 was first disclosed as SEQ ID NO: 2 in U.S. Provisional Application 60/099763, filed September 10, 1998.

Specification

The disclosure was objected to by the PTO as containing trademarks which were not capitalized and did not include the generic terminology. The specification has been amended to

include these changes. The specification has been further amended to remove reference to embedded hyperlinks.

Rejection under 35 U.S.C. §101 – Utility

The PTO has rejected Claims 1-13 as lacking a specific and substantial, or well-established utility. The PTO argues that uses such as assaying for binding partners, using polypeptides as molecular weight markers, and screening for agonists and antagonists of PRO1335 are useful only in research to determine the function of the encoded protein itself. The PTO also states that the specification does not disclose any disease or conditions known to be associated with the encoded protein, and therefore the PRO1335 polypeptide, or agonists or antagonists of PRO1335, cannot be used to prepare medicaments. Finally, the PTO states that the invention lacks a well-established utility.

Applicants respectfully disagree that they have not established a substantial and specific utility for the claimed polypeptides.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing*

a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added.)

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Utility – Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, **the PTO must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility.** Only after the PTO has made a proper *prima facie* showing of lack of utility does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Substantial Utility

Applicants have established that the Gene Encoding the PRO1335 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue and is Useful as a Diagnostic Tool

For the reasons stated below, Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish a specific and substantial utility

for the claimed polypeptides as diagnostic tools for cancer, as described in the specification, for example, at paragraph [0336].

Applicants submit herewith a copy of a declaration of J. Christopher Grimaldi, an expert in the field of cancer biology, originally submitted in a related co-pending and co-owned patent application Serial No. 10/063,557 (attached as Exhibit 1). In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal." He explains that "[t]he precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). As Mr. Grimaldi states, "If a difference is detected, this indicates that *the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes*, to screen samples to differentiate between normal and tumor." (Paragraph 7, emphasis added).

The data presented in Example 18 show that the gene encoding PRO1335 is more highly expressed in normal stomach, lung, rectal and skin tissue compared to stomach, lung, rectal, and melanoma tumor, respectively. As the Grimaldi declaration indicates, the disclosed gene and its corresponding polypeptide and antibodies are therefore useful as diagnostic tools. No additional research into how PRO1335 is related to cancer is required to use the disclosed polynucleotides, polypeptides and antibodies to distinguish tumor cells from their normal tissue counterparts. This establishes a substantial utility for the claimed polypeptides.

Applicants have established that the Accepted Understanding in the Art is that there is a Direct Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

The PTO also states that the specification does not disclose any disease or conditions known to be associated with the encoded protein. Applicants respectfully disagree.

The data Applicants report in Example 18 indicate that there are more copies of the mRNA encoding PRO1335 in normal stomach, lung, rectal and skin tissue compared to stomach, lung, rectal, and melanoma tumor, respectively. Applicants assert that it is well-established in the art that the level of protein is positively correlated to the level of mRNA. Therefore, one of

skill in the art would recognize that the PRO1335 protein is most likely more highly expressed in normal stomach, lung, rectal and skin tissue compared to stomach, lung, rectal, and melanoma tumor, respectively. This conclusion is supported by the declarations and references discussed below.

As stated above, the standard for utility is not absolute certainty, but rather *whether one of skill in the art would be more likely than not to believe the asserted utility.* The working hypothesis among those skilled in the art is that there is a direct correlation between mRNA levels and protein levels.

Applicants submit herewith a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (attached as Exhibit 2). This declaration was submitted in connection with the related co-pending and co-owned application Serial No. 10/063,557. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also submit herewith a copy of the declaration of Paul Polakis, Ph.D. (attached as Exhibit 3), an expert in the field of cancer biology, originally submitted in a related and co-owned patent application Serial No. 10/032,996. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Together, the declarations of Mr. Grimaldi and Dr. Polakis establish that the accepted understanding in the art is that there is a direct correlation between the level of mRNA and the

level of the encoded protein. Applicants submit that they have established that it is more likely than not that one of skill in the art would believe that because the PRO1335 mRNA is expressed at a higher levels in normal stomach, lung, rectal and skin tissue compared to stomach, lung, rectal, and melanoma tumor, respectively, the PRO1335 polypeptide will also be expressed at higher levels in normal stomach, lung, rectal and skin tissue compared to stomach, lung, rectal, and melanoma tumor, respectively. One of skill in the art would recognize that a gene and its encoded a protein which are differentially expressed in certain cancer cells compared to the corresponding normal tissue would have utility as diagnostic tools. Thus, Applicants submit that they have established that it is more likely than not that one of skill in the art would recognize the asserted utility of the claimed polypeptides.

The Claimed Polypeptides would have Diagnostic Utility even if there is no Direct Correlation between Gene Expression and Protein Expression

Even assuming *arguendo* that, there is no direct correlation between gene expression and protein expression for PRO1335, which Applicants submit is not true, a polypeptide encoded by a gene that is differentially expressed in cancer would **still** have a credible, specific and substantial utility.

In paragraph 6 of the Grimaldi Declaration, Exhibit 2, Mr. Grimaldi explains that:

> However, even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy.

This conclusion is echoed in the Declaration of Avi Ashkenazi, Ph.D. (attached as Exhibit 4), an expert in the field of cancer biology. This declaration was previously submitted in connection with co-pending application Serial No. 09/903,925. Applicants submit that simultaneous testing of gene expression and gene product expression enables more accurate tumor classification, even if there is no positive correlation between the two. This leads to better determination of a suitable therapy.

This is further supported by the teachings in the article by Hanna and Mornin (attached as Exhibit 5). The article teaches that the HER-2/neu gene has been shown to be amplified and/or overexpressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast

carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the overexpression of the HER-2/neu gene product (by IHC). Even when the protein is not overexpressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Applicants have established that it is the general, accepted understanding in the art that there is a positive correlation between gene expression and protein expression. However, even when this is not the case, a protein encoded by a gene that is differentially expressed in cancer would still have utility as a diagnostic tool. Thus, Applicants have demonstrated another basis of support for the utility of the claimed polypeptides.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Polypeptides

Applicants next address the PTO's assertion that the claimed polypeptides lack a specific utility. Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1335 gene in certain types of cancer cells, along with the declarations discussed above, provide a specific utility for the claimed polypeptides.

As discussed above, there are significant data which show that the gene encoding the PRO1335 polypeptide is more highly expressed in normal stomach, lung, rectal and skin tissue compared to stomach, lung, rectal, and melanoma tumor, respectively. It is well-established in the art that the encoded protein would have the same expression pattern. These data are therefore strong evidence that the PRO1335 polypeptide is associated with stomach, lung, rectal, and melanoma tumors. This is a specific utility – it is not a general utility that would apply to the broad class of polypeptides. Thus, contrary to the assertions of the PTO, Applicants submit that they have established that the asserted utilities are specific to the claimed polypeptides.

Conclusion

The PTO has asserted that the claimed invention lacks a substantial and specific utility. Applicants submit that they have established that the claimed polypeptides have both a substantial and a specific utility.

First, the Applicants provide a declaration stating that the data in Example 18 reporting higher expression of the PRO1335 gene in normal stomach, lung, rectal and skin tissue compared to stomach, lung, rectal, and melanoma tumor, respectively, are real and significant. This declaration also indicates that given the relative difference in expression levels, the disclosed nucleic acids and associated polypeptides have utility as cancer diagnostic tools.

Next, Applicants have presented the declarations of two experts in the field along with supporting references which establish that the general, accepted view of those of skill in the art is that there is a direct correlation between mRNA levels and the encoded protein levels. Thus, one of skill in the art would find that it is more likely than not that the PRO1335 proteins have utility as diagnostic tools for cancer, further supporting the asserted utility.

Applicants have also presented the declarations of two experts in the field, along with supporting references, which establish that even in the anomalous case where there is no positive correlation between gene expression and expression of the encoded protein, a protein encoded by a gene differentially expressed in cancer is useful as a diagnostic tool.

Finally, the PTO asserts that there is no asserted specific utility for the claimed polypeptides. Applicants have pointed out that the substantial utilities described above are specific to the claimed polypeptides because the gene encoding PRO1335, and presumably the PRO1335 polypeptide, are differentially expressed in certain cancer cells compared to the corresponding normal cells. The utility of a diagnostic tool for cancer is not a general utility that would apply to the broad class of polypeptides, since not all polypeptides are differentially expressed in cancer.

Thus, given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the asserted utility for the disclosed nucleic acids, polypeptides, and antibodies relating to PRO1335. In view of the above, Applicants respectfully request that the PTO withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, second paragraph – Indefiniteness

The PTO has rejected Claims 1-6, and 10 under 35 U.S.C. § 112, second paragraph, as being indefinite. The PTO objects to the recitation of "the extracellular domain ... lacking its associated signal peptide" because a signal peptide is not generally considered part of an extracellular domain.

Applicants respectfully submit that the pending claims are not indefinite as both the extracellular domain and the signal peptide regions are well-defined in the specification. In the interest of advancing prosecution of this application, Applicants will acquiesce to the PTO's assertion that a signal peptide is not normally considered part of the extracellular domain. By making this concession, Applicants understand that Claim 9, and element (c) of Claims 1-6, describe a nucleic acid sequence encoding the extracellular domain of the polypeptide of SEQ ID NO: 74, **lacking** its associated signal peptide, and Claim 10, and element (d) of Claims 1-6, describe a nucleic acid sequence encoding the extracellular domain of the polypeptide of SEQ ID NO: 74, **including** its associated signal peptide. Applicants state that this argument is made only in connection with the instant application, and does not reflect the Applicants' interpretation of any claims in any related applications.

In light of the above, Applicants request that the PTO withdraw the indefiniteness rejections under 35 U.S.C. §112, second paragraph.

Rejection under 35 U.S.C. §112, first paragraph – Enablement

The PTO rejected Claims 1-13 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. The PTO argues that because the claimed invention is not supported by a substantial, and specific utility, the claims are not enabled. The PTO has also rejected Claims 1-5 and 12-13 as not being enabled, even if the remaining claims are enabled.

As an initial matter, Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed polypeptides. Applicants therefore request that the PTO reconsider and withdraw the enablement rejection to the extent that it is based on a lack of utility for the claimed polypeptides.

The PTO asserts that even if enabling for polypeptides of SEQ ID NO: 74 are enabled, claims to less than 100% sequence identity to SEQ ID NO: 74 are not enabled because there is no

structural or functional information provided. Applicants have amended the claims to incorporate the limitation that the claimed polypeptides with less than 100% identity to SEQ ID NO: 74 must be more highly expressed in normal stomach, lung, rectal or skin tissue compared to stomach, lung, rectal or melanoma tumor respectively, or be encoded by a polynucleotide that is more highly expressed in normal stomach, lung, rectal or skin tissue compared to stomach, lung, rectal or melanoma tumor respectively. Applicants assert that techniques used to make variants of polynucleotide or polypeptide sequences are well-known to those of skill in the art (see, e.g., paragraph [0258] of the specification). Thus, the claims as amended contain sufficient structural information to enable the claims.

In view of the above arguments and amendments, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112, first paragraph – Written Description

The PTO has rejected Claims 1-5 and 12-13 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the invention.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112 , first paragraph is whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); see also *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. See e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a

number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains.

The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made. The subject matter of the pending claims concerns polypeptides having a specified sequence identity with the disclosed polypeptide sequence of SEQ ID NO: 74, and as amended, with the functional recitation: "wherein said isolated polypeptide is more highly expressed in normal stomach, lung, rectal or skin tissue compared to stomach, lung, rectal or melanoma tumor respectively, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in normal stomach, lung, rectal or skin tissue compared to stomach, lung, rectal or melanoma tumor respectively".

Based on the detailed description of the cloning and expression of variants of PRO1335 in the specification, the description of the gene amplification assay, the actual reduction to practice of sequences SEQ ID NOs: 73 and 74, and the functional recitation in the instant claims, Applicants submit that one of skill in the art would know that Applicants possessed the subject matter of the pending claims. Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

Rejection under 35 U.S.C. §102(a) – Anticipation

The PTO rejects Claims 1-10 and 14-16 as anticipated under 35 U.S.C. § 102(a) by Fujikawa-Adachi *et al.* (Genomics, 61:74-81 (1999)), which was published on October 1, 1999. The PTO states that Fujikawa-Adachi *et al.* disclose a polypeptide that is 100% identical to SEQ ID NO: 74. Applicants respectfully traverse.

Applicants submit that they are entitled to priority to U.S. Provisional Application 60/099763, filed September 10, 1998. This Provisional Application discloses the full length sequence of SEQ ID NO: 74. Applicants also submit herewith a copy of a Declaration of the co-inventors under 37 C.F.R. § 1.131 (attached as Exhibit 6), originally filed in the related co-

pending and co-owned application, Serial No. 10/063,709, which establishes that the presently claimed invention antedates the Fujikawa-Adachi *et al.* reference. The declaration and the supporting evidence submitted therewith establish conception of the invention prior to September 10, 1998, well before the October 1, 1999 publication date of the Fujikawa-Adachi reference, and diligent reduction to practice of the invention thereafter. Thus, Applicants respectfully submit that the cited reference is not available as prior art, and request that the rejections under 35 USC §102(a) be withdrawn.

Rejection under 35 U.S.C. §103(a) – Obviousness

The PTO rejects Claims 12-13 under 35 U.S.C. § 103(a) as unpatentable over Fujikawa-Adachi *et al.* (Genomics, 61:74-81 (1999)), and further in view of U.S. Patent No. 5,639,597. The PTO asserts that Fujikawa-Adachi *et al.* disclose a polypeptide that is 100% identical to SEQ ID NO: 74. However, the PTO states that Fujikawa-Adachi *et al.* do not teach chimeric polypeptides. The PTO asserts that the '597 patent teaches fusion proteins. The PTO concludes that it would be obvious to one of skill in the art to combine the teachings of Fujikawa-Adachi *et al.* and the '597 patent, and that the invention is therefore obvious in light of the prior art.

As discussed above, Applicants submit that they are entitled to priority to U.S. Provisional Application No. 60/099763, filed September 10, 1998. This Provisional Application discloses the full length sequence of SEQ ID NO: 74. The declaration of the co-inventors under 37 C.F.R. § 1.131 submitted herewith establishes that the presently claimed invention antedates the Fujikawa-Adachi *et al. et al.* reference. The declaration and the supporting evidence submitted therewith establish conception of the invention prior to September 10, 1998, well before the October 1, 1999 publication date of the Fujikawa-Adachi *et al.* reference, and diligent reduction to practice of the invention thereafter. Thus, Applicants respectfully submit that the cited reference is not available as prior art, and request that the rejections under 35 USC §103(a) be withdrawn.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Nov. 3, 2004

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